## REMARKS

Claims 1, 2, 4-8 and 12-15 are under consideration. Claims 1, 4, 5, 12, and 15 have been amended for clarity. Support is found at page 7, line 9 to page 10, line 19. Claims 2, 6, 7, 13 and 14 have been amended to have proper antecedent basis with their amended base claims. Claim 8 has been amended to delete "multipotent neuronal progenitor cells" and "committed neuronal progenitor (NP) cells". An Appendix of the now pending claims is attached for the Examiner's convenience.

Support for the amendments to Table 2 are found within Table 2; the legend of Table 2; at page 20, lines 24-27; page 23, lines 1-3; and page 25, lines 8-9. Support for the amendments to Table 3 are found at page 27, lines 1 and 26-27; and page 28, lines 2-3.

New matter has not been introduced by way of amendment. Favorable consideration of the following comments relative to the outstanding rejections as they may apply to the present claims is respectfully requested for the reasons that follow.

The Examiner maintains that the amendments to Tables 2 and 3 added July 19, 1998 constitute new matter and requires their cancellation. Applicants maintain the July 19, 1998 amendment does not add new matter to the specification because the amendments are supported by the priority application, Serial No. 60/025,597, which is incorporated by reference. Support for the incorporation of Serial No. 60/025,597 is found at page 17, lines 11-12: "All references cited herein are incorporated by reference."

Nevertheless, without admitting the propriety of the objection, Applicants have cancelled the matter added to Table 3 by the Amendment of July 19, 1999. The present amendments to Table 3 are supported by the specification, as described above.

The matter added to Table 2 by the Amendment of July 19, 1998 has not been cancelled because these amendments are supported by the specification. Support for Column 4, titled "%NP or ProNP", is found in Column 2 ("%NP (n)") and Column 3 ("%ProNP (n)"). As the title of column 4 indicates, the data shown therein is the sum of the data of Columns 2 and 3. The mean and range of the data in Column 4 is calculated in the manner practiced in the art and as done for the data of Columns 2 and

3. The mean is the average of the results of Experiments 1 and 2; and the range is the difference between the mean and results of Experiments 1 and 2. In preparing this amendment, Applicants noticed a typographical error in the mean reported in column 4. The mean of 33% and 40% is 36.5%, rather than 38.5%. Column 4 has been amended accordingly.

Support for Table 2, column 5, "%NNP (n)", is found at page 25, lines 8-9 and in the legend of Table 2. Briefly, page 25, lines 8-9 provides the percentage of NNPs in Experiments 1 and 2. The "n" values of column 5 are calculated from the procedure followed in Experiments 1 and 2. "A total of 144 cells were examined in experiment 1 and 224 cells in experiment 2." (*see* Table 2, legend). Page 23, lines 1-3, states that the purpose of the experiment that yielded the results shown in Table 2 was to: "determine the functional properties of the morphologically undifferentiated subset of $RET^+$ cells...." The undifferentiated $RET^+$ cells or flat cells (page 20, lines 24-27), are disclosed in the legend of Table 2 as being of three types: neuronal progenitors, proneural progenitors or nonneuronal progenitors:

> Single $RET^+$ cells were identified 15 hr after plating and observed 24 hr for the next 4 days. All of the cells initially circled survived this incubation. At the end of this incubation, they were classified as neuronal progenitors (NPs), proneural progenitors (ProNPs) or nonneuronal progenitors (NNPs).

Therefore, all of the undifferentiated, $RET^+$, flat cells were identified as being one of these three progenitors. The "n" values in column 5, which is the number of NNP cells, can be calculated by subtracting the number of NP and ProNP cells from the total number of cells in each experiment. For Experiment 1, the number of NNP cells is: 144 - (25+23) = 96. For experiment 2, the number of NNP cells is: 224 - (78+11) = 135.

Based on the foregoing amendments and remarks, Applicants respectfully assert that the amendments to Tables 2 and 3 do not comprise new matter and respectfully request the Examiner to withdraw the objection.

Claims 1-2, 4-7 and 12-15 stand rejected under 35 U.S.C. § 112, second paragraph. The Examiner contends the metes and bounds of "RET antigen" cannot be

determined. The Examiner acknowledges that "RET antigen" is defined in the specification as "All or part of a sequence of RET" (page 7, lines 12-14) but maintains the claims are not limited to this definition. In response to Applicants' position that the sequence of RET is incorporated by reference at page 7, lines 9-11, the Examiner states that essential material cannot be incorporated by reference to a publication. Applicants respectfully traverse the rejection.

Without admitting the propriety of the rejection, the term "RET antigen" has been deleted from the claims and replaced with "all or part of the RET protein".

Regarding the Examiner's position that the incorporation of the RET sequence by reference is improper, Applicants respectfully assert that the RET sequence is known in the art and is easily obtained by the skilled artisan.

In view of these amendments and remarks, Applicants respectfully request the rejection be withdrawn.

Claims 1-2, 4-8 and 12-15 stand rejected under 35 U.S.C. §102(a) as being anticipated by Lo *et al.* 1995. Neuron 15:527-539 and under 35 U.S.C. §102(f)/(g). Applicants respectfully traverse the rejections.

With the documents submitted herein in accordance with 37 CFR §1.48(a), David Anderson and Li-Ching Lo are now the inventors of the instant application. In view of the amended inventorship, the rejections under §102(a)/(f)/(g) are rendered improper and Applicants respectfully request they be withdrawn.

Claim 8 stands rejected under 35 U.S.C. §102(b) as being anticipated by Stemple *et al.* 1992. Cell 71:973-985. The Examiner contends that Stemple *et al.* disclose a substantially pure population of neuronal progenitor (NP) cells. Applicants respectfully traverse the rejection.

Without admitting the propriety of the rejection, "committed neuronal progenitor (NP) cells" has been deleted from the Markush group of Claim 8. Applicants respectfully request the rejection be withdrawn.

Claim 8 stands rejected under 35 U.S.C. § 102(b) as being anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as obvious in view of Vescovi *et al.* Applicants respectfully traverse the rejection.

Vescovi *et al.* report the continual proliferation of EGF-dependent progenitor cells that differentiate into neurons and nonneuronal cells (astrocytes). Although not expressly stated by the Examiner in the Advisory Action or the Final Rejection, the Examiner's position appears to be that the EGF-dependent progenitor cells anticipate or render obvious the instantly claimed multipotent neuronal progenitor (proNP) cells which differentiate into neurons and nonneuronal cells (see page 23, lines 1-22).

Without admitting the propriety of the rejection, "multipotent neuronal progenitor (proNP) cells" has been deleted from Claim 8. As Vescovi *et al.* do not disclose another cell type, Applicants respectfully assert that the reference does not anticipate or render amended Claim 8 obvious. Applicants respectfully request the rejection be withdrawn.

Claim 8 stands rejected under 35 U.S.C. § 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious in view of Reynolds *et al.* Soc. Neurosci. Abstr. 18:1107, Abstract 467.3, 1992. Applicants respectfully traverse the rejection.

Reynolds *et al.* report the differentiation of EGF-responsive progenitors into neurons and astrocytes. Although not expressly stated by the Examiner in the Advisory Action or the Final Rejection, the Examiner's position appears to be that the EGF-dependent progenitor cells anticipate or render obvious the instantly claimed multipotent neuronal progenitor (proNP) cells which differentiate into neurons and nonneuronal cells (see page 23, lines 1-22).

Without admitting the propriety of the rejection, "multipotent neuronal progenitor (proNP) cells" has been deleted from Claim 8. As Reynolds *et al.* do not disclose another cell type, Applicants respectfully assert that the reference does not anticipate or render amended Claim 8 obvious. Applicants respectfully request the rejection be withdrawn.

Claim 8 stands rejected under 35 U.S.C. § 102(e) as being anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as being obvious in view of Boss *et al.* (U.S. Patent No. 5,411,883). Applicants respectfully traverse the rejection.

Boss *et al.* describe a method of isolating and proliferating neuron progenitor cells which differentiate into neurons and glia (Column 6, lines 9-12): "Over time, cells begin to migrate from these structures and form typical two-dimensional monolayers in which differentiating neurons and glia can be observed." Although not expressly stated by the Examiner in the Advisory Action or the Final Rejection, the Examiner's position appears to be that the neuron progenitor cells of Boss *et al.* anticipate or render obvious the instantly claimed multipotent neuronal progenitor (proNP) cells which differentiate into neurons and nonneuronal cells (see page 23, lines 1-22).

Without admitting the propriety of the rejection, "multipotent neuronal progenitor (proNP) cells" has been deleted from Claim 8. As Boss *et al.* do not disclose another cell type, Applicants respectfully assert that the reference does not anticipate or render amended Claim 8 obvious. Applicants respectfully request the rejection be withdrawn.

Claims 1-2, 4-8, and 12-15 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Lo *et al.* 1994. Perspectives Dev. Neurobiol. 2:191-201, 1994, Stemple *et al.* 1993 Dev. Biol. 159:12-23 (Stemple '93), Stemple *et al.* 1992. Cell 71:973-985 (Stemple '92), and Martucciello *et al.* for reasons of record. Applicants respectfully traverse the rejection.

Lo *et al.* postulate that $RET^+$ uncommitted neural crest cells "undergo an early segregation into sensory, autonomic, and glial lineages...." and diagram their proposed pathways of neural crest development (Figure 6). However, Lo *et al.* do not support a conclusion of obviousness because the putative progenitor cells of Lo *et al.* do not teach or suggest the progenitors of the present invention. For example, the nonneuronal progenitor (NNP) cells of the present invention are $RET^+$ and differentiate into "glial cells and possibly other as yet unidentified nonneuronal cells." (page 25, lines 7-8). In contrast, the glial progenitors of Lo *et al.* apparently do not express RET and Lo *et al.* are silent with respect to the differentiation of these cells. The disclosed proneuronal progenitor (NNP) cells give rise to neurons, glial cells, and other unidentified nonneuronal cells (page 23, and 18-19), whereas, none of the progenitor cells of Lo *et*

*al.* give rise to these cell types. Lastly, the disclosed neuronal progenitor (NP) cells, only differentiate into neurons (page 25, lines 10-12). In contrast, Lo *et al.* do not propose a progenitor that differentiates in this manner. Lo *et al.* propose that the autonomic progenitor differentiates into neurons and chromaffin cells and is silent with respect to the differentiation of the sensory progenitor. Therefore, distinct and fundamental differences exist between the claimed progenitors and the putative cells of Lo *et al.*

The above analysis also indicates that Lo *et al.* teach away from the claimed invention. Lo *et al.* indicate that glial progenitors do not express RET; however, the glial progenitors of the present invention, the NNP cells, are $RET^+$. The courts have ruled that a reference which leads one of ordinary skill in the art away from the claimed invention cannot render the claimed invention unpatentably obvious. See Dow Chemical Co. v. American Cyanamid Co., 2USPQ 2d 1350 (Fed. Cir. 1987). In addition, "[T]he question under 35 USC § 103 is not merely what the references expressly teach but what they would have suggested to one of ordinary skill in the art at the time the invention was made." *In re* Lamberti, 192 USPQ 278, 280 (CCPA 1976). See also *In re* Burckel, 201 USPQ 67, 70 (CCPA 1979). In view of these decisions, Applicants respectfully assert that Lo *et al.* teach away from the claimed invention and cannot support a legal conclusion of obviousness.

The Examiner contends that Lo *et al.* provide the motivation to practice the claimed invention by suggesting that cells expressing RET should be isolated for further testing. Applicants respectfully assert this statement does not teach or suggest the progenitor cells of the present invention and does not enable their isolation or use. The Examiner is respectfully reminded that to support a conclusion of obviousness under 35 U.S.C. § 103, the prior art must enable a skilled artisan to make and use the claimed invention. In *In re Payne*, 203 USPQ 245, 255 (CCPA 1979) the CCPA stated:

> [r]eferences relied upon to support a rejection under 35 U.S.C. § 103 must provide an enabling disclosure, i.e., they must place the claimed invention is possession of the public. *In re Brown*, 51 CCPA 1254, 1259 329 F.2d 1006, 1011, 141 USPQ 245, 249 (1964). An invention is

> not "possessed" absent some known or obvious way to make it. *In re Hoeksema*, 55 CCPA 1493, 1500, 399 F.2d 209, 274, 158 USPQ 596, 601 (1968).

The Examiner is also respectfully directed to *Minnesota Mining and Manufacturing Company v. Blume*, 215 USPQ 585 (CCPA 1982) where the CCPA stated:

> [t]he enabling disclosure concept is a commonsense factor in making a determination of obviousness, for if neither any item of prior art, nor the background knowledge of one with ordinary skill in the art, would enable one to arrive at an invention, that invention would not be obvious.

Rather than teaching or suggesting the progenitor cells of the claimed invention, Applicants respectfully assert that the Lo *et al.* reference is not enabling but is merely an invitation to experiment. An invitation to experiment may support an obvious to try rationale but the M.P.E.P. §2145.X.B. outlines, an obvious to try rationale is not the standard under §103. Case law also is clear that the obvious to try criterion is not sufficient to support a conclusion of obviousness. *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988). In *The Gilette Co. v. S.C. Johnson & Son, Inc.*, 16 USPQ2d 1923 (Fed. Cir. 1990) the court ruled that:

> "[a]n "obvious to try" situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued."

Therefore, the statement of Lo *et al.* that $RET^+$ cells should be isolated for further experimentation may stimulate a scientist's curiosity but the statement does not teach how to obtain the progenitor cells of the present invention or that these progenitors would be obtained if certain directions were pursued.

The secondary references also do not teach or suggest the progenitor cells of the present invention and, as such, do not add to the disclosure of Lo *et al.* Stemple '93 teach developmental heterogeneity in neural crest cells and methods for their analysis. Stemple '92 is limited to fluorescence activated cell sorting. Martucciello *et al.* describe a monoclonal antibody bound to a RET antigen on a neuron. Therefore, the

references relied upon by the Examiner, either alone or in combination, at least do not teach or suggest the progenitor cells of the present invention.

The M.P.E.P. § 2143 outlines three basic criteria that must be met in order to establish a *prima facie* case of obviousness: i) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; ii) there must be a reasonable expectation of success; and iii) the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Therefore, to establish a conclusion of obviousness, the prior art must not only teach or suggest all the claim limitations but must also teach or suggest the desirability of the claimed invention and provide a reasonable expectation of success. A conclusion of obviousness can not be established if the prior art does not fulfill any one of these criteria.

As set forth above, none of the references, either alone or in combination, teach or suggest the progenitor cells of the claimed invention and, therefore, do not teach or suggest all the claim elements. Moving to the issue of whether the disclosures suggest that the elements be combined, Applicants respectfully submit that the elements are not disclosed; therefore, there can be no suggestion that they be combined. Lastly, because the first and third criteria have not been met, there can be no reasonable expectation of success.

In view of these remarks and amendments, Applicants respectfully assert that none of the references, either alone or in combination, meet the requirements for establishing a *prima facie* case of obviousness. Applicants respectfully request the Examiner to withdraw the rejection.

## CONCLUSION

Applicants respectfully submit that the claims are now in condition for allowance and an early notification of such is solicited. If the Examiner believes a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned attorney.

Respectfully submitted,

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APPENDIX:

1. (Twice amended) A composition comprising a monoclonal antibody [specifically bound to a RET antigen on]and a cell selected from the group consisting of a multipotent neuronal progenitor (proNP) cell, a nonneuronal progenitor (NNP) cell and a committed neuronal progenitor (NP) cell, wherein said monoclonal antibody is specifically bound to all of part of the RET protein on said cell.

2. (Twice Amended) The [monoclonal antibody]composition according to claim 1, wherein said [RET antigen]protein consists essentially of the extracellular domain of RET.

4. (Twice Amended) A method for the enrichment of neural progenitor cells, said method comprising:

a) combining a mixed population of cells comprising neural-crest derived cells comprising neural progenitor cells with [a reagent]an antibody that specifically binds to [a]all of part of the RET protein [antigen]; and

b) selecting for RET positive cells.

5. (Amended) [A]The method according to claim 4 wherein said [reagents are antibodies] antibody is selected from the group consisting of polyclonal antibody, monoclonal antibody, antibody fragments, and single chain antibody.

6. (Amended) [A]The method according to claim 5, wherein [at least one of] said [antibodies]antibody is fluorochrome conjugated.

7. (Twice Amended) A method according to claim 6, wherein said selecting with said fluorochrome conjugated [antibodies]antibody is by flow cytometry.

8. (Twice Amended) A substantially pure population of neural crest derived neural progenitor cells where said cells are [selected from the group consisting of multipotent

neuronal progenitor (proNP) cells,] nonneuronal progenitor (NNP) cells [and committed neuronal progenitor (NP) cells].

12. (Amended) [A]The population according to claim 8 wherein said neural progenitor cells are bound to [a reagent]an antibody that specifically binds to RET [antigen]protein.

13. (Amended) [A]The population according to claim 12 wherein said [reagent is a RET] antibody is selected from the group consisting of polyclonal antibody, monoclonal antibody, antibody fragments, and single chain antibody.

14. (Amended) [A]The population according to claim 13 wherein said antibody is a monoclonal antibody.

15. (Amended) A method for the enrichment of neural progenitor cells, said method comprising:

a) combining a mixed population of cells comprising neural-crest derived cells comprising neural progenitor cells with a monoclonal antibody that specifically binds to [a]all of part of the RET protein [antigen]; and

b) selecting for RET positive cells.